UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,618	09/19/2008	Antonino Cattaneo	128.1008	5926

20311 7590 04/01/2011

LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER
NOAKES, SUZANNE MARIE

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
04/01/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/583,618	CATTANEO ET AL.	
	Examiner	Art Unit	
	SUZANNE NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8-24* is/are pending in the application.

4a) Of the above claim(s) *8-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Colored Drawings Notice*.

DETAILED ACTION

Status of Claims

1. Claims 1, 2 and 8-24 are pending. Claims 8-23 remain withdrawn from further and claims 1, 2 and 24 are subject to examination the merits.

Drawings

2. The colored Drawings petition filed 12/27/2010 has been Granted – see attached.

Withdrawal of Previous Objections/Rejections

3. The objection to the specification is withdrawn in view of the amendments to include a “Brief Description of the Drawings” section in the application.

4. The objections to the claims for grammatical formalities is withdrawn in view of the claim amendments.

5. The rejection of claims 1, 2 and 24 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendments to claims which match the preamble to the conclusion.

6. The rejection of claims 1, 2 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen et al. (U.S. Pat. No. 5,693,761) in view of Ramslund et al. (J. Mol Recognition, 2002, 15:248-259 - cited on IDS of 09/13/2007) is withdrawn in view of Applicants arguments. Specifically there is no express or implied teaching anywhere of calculating the RMSD's of the compared frameworks.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 2 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen et al. (US 5,639,641) in view of Ramsland et al. (J. Mol Recognition, 2002, 15:248-259 - cited on IDS of 09/13/2007).

The rejection was recited previously and is reiterated below for convenience.

Pedersen et al. teach humanizing a rodent antibody (Ab) or fragment by resurfacing said antibody wherein the method comprises:

(a) determination of the conformational structure of the variable region of the rodent Ab or fragment by constructing a 3D model of the rodent Ab variable region;

(b) generating sequence alignments from relative accessibility distributions from X-ray crystallographic structures of the rodent Ab variable region heavy and light chains to give a set of heavy and light chain framework positions;

(c) defining a set of heavy and light chain surface exposed amino acid residues using the set of framework positions generated in (b);

(d) identifying from human antibody amino acid sequences a set of heavy and light chain surface exposed amino acid residues that is most closely identical to the set of residues defined in (c);

(e) substituting the set of heavy and light chain surface exposed amino acid residues defined in (c) with the set of residues identified in (d);

(f) constructing a 3D model of the rodent antibody variable region resulting from the substitution of (e);

(g) identifying by comparing the 3- D models any amino acid residues from the set identified in (d), that are within 5 Å of any atom of any residue of the complementarity determine regions (CDRs) of the rodent Ab to be humanized – see Figure 6 and Example 2, wherein a LSQ operation is performed; and

(h) changing/retro-mutating any residue identified in (g) from the human to the original rodent amino acid residue.

It is noted that step (a) need not be conducted first, but must be conducted prior to step (g).

Pedersen et al., however, do not teach the method wherein the rodent antibody molecular model has been determined crystallographically either *ab initio* or alternatively obtained from the protein databank (PDB).

Ramsland et al. teach the comparison of crystal structures of humanized and mouse-human chimeric Fab antibodies (resolution 2.6Å). It is noted that in 2002 (the time of publication) there were more than 300 crystallographically determined antibody structures determined and found in the protein databank (PDB), 50 of those are different human Immunoglobulins (see Introduction). Crystallographic structures were obtained from the PDB with resolution limits of 2.6Å or better and/or a *R*-cryst of 21% ensuring high quality structural comparisons (See Table 1, p. 254). These comparisons allowed the identification of amino acids residues in the acceptor framework regions which could be retro-mutated to the corresponding donor framework region to restore the shape of the binding site in the acceptor antibody (see pg.255, 2nd col., last paragraph to pg.256 1st col., 1st paragraph and Figure 6). Ramsland et al. conclude that comparison of the three dimensional crystal structures allows the identification of structural differences for antibody engineering, especially in the development of humanized antibodies (see Conclusion, pg.256 2nd col., last paragraph, to pg.257).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Pedersen et al. method by utilizing crystallographic structures as the starting models for rat antibodes as taught in Ramslund et al. in the process rather than molecular models. As noted by Ramslund et al., there were 300 antibody crystallographic structures found within the PDB at the time of publication and thus a variety of starting models could be chosen. One skilled in the art would be

motivated to make such a substitution because the crystallographic models are seen as a more accurate and true reflection of the antibodies which are concerned and to be humanized and thus will likely produce better results. One skilled in the art furthermore would have a reasonable expectation of success in doing so because Ramslund et al. teaches that upon comparing crystallographic structures, residues that need to be changed and were not expected to necessarily need changing could be identified by the structural comparisons.

Therefore when the references are taken together, the instant claims are deemed as *prima facie* obvious.

Applicants Remarks and Examiner's Rebuttal:

It is noted that Applicants seem to recognize that the 2nd 35 USC 103(a) rejection of record as recited in the previous Office action, Section 13 is Pedersen in view of Ramsland – Remarks, p. 20, 4th para. However, Applicants subsequently make all of their counter-remarks and arguments to this rejection as if said rejection was Queen in view of Pedersen - see last paragraph of p. 20 to p. 21. For instance, Applicants assert that Pedersen do not remedy the deficiencies of Queen (see p. 20, last line) and that "Pedersen nowhere would have taught or suggested to the artisan that the method of Queen could be modified to produce the method as recited by claim 1." – see p. 21, lines 4-5. However, as noted, the rejection was to Pedersen in view of Ramsland. As much of the response taken together does not fit the rejection, the Examiner will attempt to address the noted deficiencies.

With the limited remarks made to Pedersen et al., it is noted that the method utilizes 3-D models such as homology models rather than crystallographic models as the initial starting model, and according to Pedersen et al. this has more to do with there

being so few antibody structures to begin with and that it is well known in the art (at the time of their invention) and thus use molecular modeling programs to produce an starting desired antibody model to model into.

To build the framework model as in parts b and c of the instant claims, the following is performed (see Example 2 and Figure 6) for comparison purposes:

> the Framework Region
>
> Antibody framework regions consist of conserved .beta.-strands that form the .beta.-barrel structure characteristic of immunoglobulin V-type regions. In the procedure described here each V-region is built from a database of known antibody structures, using sequence homology for selection of the light (L) and heavy (H) chain V-domains. *The two domains are then paired by least squares fitting on the most conserved strands of the antibody .beta.-barrel (Table 2 and FIGS. 5 & 6).* The strand orientations were determined by analyzing the barrels of known antibody crystal structures. Eight antibodies were analyzed using a multiple structure fitting program as follows. Seven structures were fitted onto one of the set selected at random and mean coordinates were calculated. All eight structures were then fitted onto these mean coordinates and new mean coordinates determined. This procedure was iterated until the mean coordinate set converged (5-10 cycles). The variance for the mean coordinates at each barrel point (N,C.alpha.,C) was calculated. In FIG. 5 this variance is plotted against the projected positions of these points onto the conjugate axis of the barrel.
>
> Strand 8 and all but two residues of strand 7 in both light and heavy chains were eliminated as they showed deviations greater than 3.sigma. (standard deviation units) from the mean coordinates. These two strands comprised the takeoff points of CDR H3, and suggests that any knowledge-based prediction of CDR H3 would have to account not only for sequence and length variation in the CDR itself, but also for the position of the participating strands. The remaining mean coordinates were used as a scaffold onto which the L and H chains were fitted. Strands 7 and 8 in the final framework were obtained from the database structure used in the construction. The framework strands are marked + in the multialignment in Table 2.
>
> The sidechains were then replaced using a . `maximum overlap` method, in which sidechain templates were fitted on backbone atoms with the sidechain torsion angles being adjusted to match those of equivalent torsions in the parent sidechain.

While not expressly stated using the terminology root mean square deviation, it is very well known in the art that that said RMSD is calculated using a least-squares fitting. Thus, the framework model is produced similarly with the exception that the mouse

model was not produced crystallographically. Ramsland et al. remedies that deficiency by noting that utilizing already solved, three-dimensional structures has significant benefits and they too suggest high resolution structures from 1.6Å to 2.6Å - see Table 1 and that there are significantly more (+300) antibody structures which can be utilized from the PDB as of 2002.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1, 2 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 24 of copending Application No. 12/838,062. Although the conflicting claims are not identical, they are not patentably distinct from each other because the two claims sets are identical except for the instant claims are drawn to a genus of any or all animal anibodies used in the methods, whereas the '062 application is drawn to the specific antibody anti-NGF. This, however, is notably a preferred embodiment of the instant application and as such, the claims overlap in scope to such an extent that they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants Remarks:

Applicants have held that said rejection be held in abeyance until such time that allowable subject matter is indicated. Said request is acknowledged.

References of Interest – Not Relied Upon – cited previously

11. Tamura et al (2000) Structural correlates of an anti-carcinoma antibody: identification of specificity-determining residues (SDRs) and development of a minimally immunogenic antibody variant by retention of SDRs only. J. Immunol. 164:1432-1441. This reference has the premise that increasing the proportion of characteristically human sequence in a humanized antibody will reduce that antibody's immunogenicity, and accordingly disclose methods for grafting partial CDR sequences. Determination of the three-dimensional structure of antibody-antigen complexes showed that many residue positions assigned to the CDRs defined by Kabat and Wu rarely were directly involved in antigen binding.

12. Harris et al. (EP 0 578 515 A2 – cited on IDS of 03/17/2010).

Harris et al. teach producing a humanized monoclonal antibody (MAb) by utilising a process of comparative model building by utilizing known 3-D structures as determined crystallographically comprising:

(a) selecting a monoclonal antibody to be humanized, such as a murine antibody;

(b) searching computer databanks for protein crystal structures demonstrating more than 50% sequence homology to the variable region of said antibody to produce a structural template;

(c) determining the structure of the CDR region loops and assigning the loops to cononical loop conformations;

(d) determining the framework (F) residues crucial to CDR loop conformation;

(e) replacing the CDR loops of structural templates with cononical CDR backbone templates using interactive computer graphics;

(f) searching computer databanks to extract initial backbone approximations (e.g. root–mean-square deviations (RMS)) for each loop for non-cononical loops;

(g) replacing non-conserved amino-acid side chains in similar positions on the antibody and on the computer model with human residues using interactive computer graphics to produce a model having a combination of backbone fragments of different antibodies with replaced side chains;

(h) solvating the models with a water layer corresponding to approx. 7Å;

(i) refining the structure with an energy minimization protocol to produce a structure wherein all atoms of the system are freely mobile;

(j) searching computer databanks to find homologous human sequences for the variable light and variable heavy chains;

(k) combining the sequences in (j) to obtain human templates;

(l) comparing the structural template of (a) with the human templates of (k) and selecting a human template with variable regions having more than 50% sequence identity with the structural template;

(m) determining the CDR loops of the human template selected in (l);

(n) replacing the CDR loop region of the selected human template with the analogous sequences from the antibody to produce a phase I humanized sequence;

(o) superimposing the Ab models and phase I humanized sequence to compare binding site regions;

(p) identifying by the comparison in (o), all amino acids in the framework residues and CDR junction residues which interact with the antibody CDR loops that can be important to structural integrity of the antibody binding sites (ABS);

(q) reinserting into the phase I humanized sequence all residues identified in (p) to be different from those in the Ab, and refining the resultant structure with an energy minimisation protocol, to produce a phase II humanized sequence;

(r) refining the phase II humanized sequence using interactive conformational search protocols on all regions of the ABS and by analysis of the ABS to determined which regions of the CDR surface or CDR-framework region are not likely to involve antigen (Ag) binding; and

(s) replacing (e.g. retromutating) the residues in the non-antigen binding regions of the ABS with residues corresponding to human residues, to produce a humanized MAb. (see claims 1 and 2 and pp. 4-6).

It is noted that backbone comparisons of initial structures should have RMS deviations of less than 3Å (see Example 1, p. 10-11).

Conclusion

13. No claim is allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656
23 March 2011